REMARKS

The Examiner has noted that Applicant has not filed a certified copy of the priority document. Applicant submits herewith a certified copy of Great Britain Patent Application No. 9708526.0.

On page 4 of the Office Action, the Examiner indicates that claim 40 has been withdrawn form consideration, however, the Examiner has included claim 40 in all of the rejections set forth. The subject matter of claim 40 is closely related to the subject matter of claim 31 from which claim 40 depends. Thus, Applicant asserts that claim 40 has been indicated as withdrawn by mistake.

By this amendment, claims 31 and 58 have been amended to delete recitation of a polynucleotide sequence "which is expressed to generate a therapeutic product which is an RNA."

Claims 36-39, 43-50, 52-57, 63-66, 70-77, and 79-96 have been cancelled without prejudice to Applicant's right to pursue the cancelled subject matter in this or related applications. The Examiner has indicated that claim 31 is a linking claim. Upon allowance of claim 31, Applicants reserve the right to pursue claims corresponding to the cancelled claims of Groups I, II, and IV to VI, in this or other applications.

Claims 31-35, 40-42, 51, 58-62, 67-69, and 78 will be pending upon entry of this amendment in the instant application. Applicant respectfully requests that the amendments and remarks made herein be entered into the record of the instant application.

1. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR ENABLEMENT

Claims 31, 32-35, 40-42, 49-51, 58-62, 67-69, and 76-78 remain rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enabling support in the specification for a plasmid vector comprising a myosin light chain enhancer and a viral promoter operably linked to a sequence that generates a therapeutic RNA.

Without acquiescing to the basis of the Examiner's rejection and solely in the interest of advancing prosecution, claims 31 and 58 have been amended to delete a sequence that generates a therapeutic RNA and claims 49, 50, 76, and 77 have been cancelled, without prejudice to Applicant's rights to pursue the cancelled subject matter in this or related applications.

In view of the foregoing amendments, Applicant submits that the rejection for

indefiniteness under 35 U.S.C. §112, first paragraph, has been overcome and should be withdrawn.

2. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR WRITTEN DESCRIPTION

Claims 31, 32-35, 40-42, 49-51, 58-62, 67-69, and 76-78 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. In particular, the Examiner contends that the specification fails to provide adequate written description support for a representative number of species of RNA therapeutic products.

Without acquiescing to the basis of the Examiner's rejection and solely in the interest of advancing prosecution, claims 31 and 58 have been amended to delete a sequence that generates a therapeutic RNA and claims 49, 50, 76, and 77 have been cancelled, without prejudice to Applicant's rights to pursue the cancelled subject matter in this or related applications.

In view of the foregoing amendments, Applicant submits that the rejection for indefiniteness under 35 U.S.C. §112, first paragraph, has been overcome and should be withdrawn.

3. THE REJECTION UNDER 35 U.S.C. § 102(a), FOR ANTICIPATION

Claims 31, 32-35, 40-42, 51, 58-62, 67-69 and 78 have been rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Novo et al. (1997, Gene Therapy 4:488-492, hereafter "Novo").

The present application claims the benefit of Great Britain Patent Application No. 9708526.0, filed April 25, 1997, a certified copy of which is submitted herewith. As Novo was published May 2, 1997, subsequent to the instant application priority date, it is not prior art under 35 U.S.C. § 102(a). Thus, the rejection under 35 U.S.C. §102(a) in view of Novo is improper and should be withdrawn.

Claim 31 has been rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Ohshima et al. (1997, PNAS 94:2540-2544, hereafter "Ohshima").

Applicants invite the Examiner's attention to the Declaration under 37 C.F.R. § 1.131 of Geoffrey Goldspink submitted herewith. The Declaration of Dr. Goldspink establishes invention of the claimed subject matter prior to the effective date of Ohshima as a prior art reference. Thus, the rejection under 35 U.S.C. §102(a) in view of Ohshima should

be reconsidered and withdrawn.

In view of the foregoing remarks, Applicant submits that neither Novo or Ohshima anticipate the claimed invention under 35 U.S.C. §102(a) and respectfully submit that the rejections should be withdrawn.

4. THE REJECTION UNDER 35 U.S.C. § 102(e), FOR ANTICIPATION

Claim 31 has been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Weiner et al. (U.S. Patent No. 5,830,876, issued November 3, 1998, hereafter "Weiner").

Applicant disagrees. Weiner teaches methods for immunizing an individual against a pathogen by injection of a sequence that encodes a target protein operably linked to regulatory elements needed for gene expression. Weiner does not describe the use of vectors which include either a myosin heavy chain promoter or a viral promoter in combination with a myosin light chain enhancer to control expression of a therapeutic protein. Furthermore, Weiner does not describe the use of a viral strain as an expression vector and in fact teaches away from the use of a viral strain comprising an expression cassette. Thus, Wiener neither teaches use of a myosin light chain enhancer or a viral strain comprising an expression cassette. Weiner does not disclose each and every element of the claimed method and therefore does not anticipate the claimed methods.

In view of the foregoing remarks, Applicant respectfully submits that the rejection for anticipation under 35 U.S.C. §102(e) is improper and should be withdrawn.

5. THE REJECTION UNDER 35 U.S.C. § 103(a), FOR OBVIOUSNESS

Claims 35, 40, 62, and 67 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Weiner in view of Donoghue et al. (1988, Genes Dev 2:1779-1790, hereafter "Donoghue") and Steffy and Weir (1991, J. Virol. 65:6465-6460, hereafter "Steffy and Weir").

A finding of obviousness under 35 U.S.C. §103 requires a determination of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed subject mater and the prior art; and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1966).

The relevant inquiry is: (1) whether the prior art suggests the invention; and

(2) whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The Federal Circuit has also stated time and again that one cannot consider a reference in less than its entirety, i.e., disregard disclosures in the reference that diverge from and teach away from the invention. Specifically, the Federal Circuit, stated, "It is impermissible within the framework of a Section 103 rejection to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the reference fairly suggests to one of ordinary skill in the art". *In re Wesslau*, 353 F.2d 238, 241 (CPCA 1965).

In the present instance, Applicant submits that one skilled in the art would have had no motivation to combine the teachings of the cited references and no reasonable expectation of achieving success in combining the teachings of the references. The claimed methods comprise use of a combination of a myosin light chain enhancer and a myosin heavy chain or viral promoter to drive expression of a therapeutic polypeptide where the expression cassette is administered in a virus for effective treatment of a human or animal body.

Donoghue discloses the nucleotide encoding sequence of an enhancer derived from the myosin light chain 1/3 gene locus. Steffy and Weir disclose infection of Vero cells *in vitro* with recombinant viruses which have promoter element fragments of the herpes simplex virus 1 (HSV) operably linked to β-Galactosidase (see page "construction of plasmids" section on pages 6454 and 6455). The results indicate that the HSV promoter elements are capable of driving expression of β-Galactosidase *in vitro*. Neither Donoghue or Steffy and Weir suggest treatment of a human or animal body or how to achieve levels of expression *in vivo* that would be therapeutically effective.

Weiner teaches methods for immunizing an individual against a pathogen by direct intramuscular injection of a plasmid that encodes a target protein operably linked to regulatory elements needed for gene expression. Weiner fails to describe or suggest the use of a myosin light chain enhancer or the use of a viral strain as an expression vector for the expression of a therapeutically effective polypeptide. One skilled in the art would not have found motivation to combine the described method of Wiener and use the myosin enhancer of Donoghue and the HSV promoter of Steffy and Weir in an expression cassette and administer the expression cassette in a viral strain comprising said expression cassette because Weiner suggests that direct injection of plasmids is preferable to administration in a virus and neither

Donoghue or Steffy and Weir suggest combining viral promoters with myosin enhancers or treatment using recombinant viruses.

Even if one skilled in the art were to combine the described therapeutic method of Wiener and use the myosin enhancer of Donoghue and the HSV promoter of Steffy and Weir, the skilled artisan would not have had a reasonable expectation of success. The Applicant was the first to discover that combining a myosin light chain enhancer in an expression cassette with a viral or myosin heavy chain promoter and a polynucleotide encoding a therapeutic polypeptide to drive expression of said polypeptide resulted in expression and secretion of correctly glycosylated polypeptide. In particular, it is the instant application that described an expression cassette comprising the mysosin light chain 1/3 enhancer and the CMV viral promoter to drive expression of a α-Galactosidase resulted in the expression and secretion of correctly glycosylated α-Galactosidase from differentiated muscle cells (see page 13, line 15 through page 14, line 7 of the instant application). The correct expression of a therapeutic polypeptide demonstrates the effectiveness of the claimed methods of treatment, because a correctly glycosylated polypeptide will exhibit the same functional biological properties as a natively produced polypeptide. Absent the data disclosed by the Applicant, one skilled in the art would not have reasonably expected that the claimed combination of promoter and enhancer would result in expression of a therapeutic polypeptide with properties that are beneficial for treatment efficacy. Thus, the subject matter as a whole would not have been obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, Applicant submits that the unexpected results achieved using the claimed combination of enhancer and promoter are sufficient to rebut the *prima facie* obviousness rejection. In addition to the surprising results described above in relation to proper expression of a polypeptide, the specification also discloses *in vivo* experiments where expression cassettes comprising a myosin heavy chain promoter and a myosin light chain enhancer operably connected to the CAT reporter gene were administered in plasmids to mice (see page 19, line 21 through page 20, line 9 of the instant application). The results demonstrate that the specific combination of enhancer and promoter unexpectedly increased expression by 4-fold in comparison to expression constructs where the myosin light chain enhancer was excluded from the expression cassette. In another experiment, Applicant demonstrated that unexpectedly high levels of expression could be achieved using the claimed combination of myosin light chain enhancer with the CMV viral promoter to drive expression of α-Galactosidase in a mouse model for Fabry's disease which lacks α-

Galactosidase expression (see page 15, line 20 through page 16, line 24 of the instant application). The results demonstrate that the units of α-Galactosidase activity in muscle per mg protein increased from 4-5 units (levels in normal mice) up to between about 96 and about 706 units in the mice having the expression cassette. This increase is reflective of the surprising expression levels achieved *in vivo* using the claimed combination of myosin light chain enhancer and a viral promoter.

In view of the foregoing remarks, one skilled in the art would not have found a motivation to combine the teachings of Steffy and Weir, Donoghue, and Wiener or a reasonable expectation of success. Moreover, the results achieved by the Applicant using the combination of a myosin light chain enhancer and a viral or myosin heavy chain promoter were unexpected and are sufficient to rebut the obviousness rejection.

Applicant submits that the rejection under 35 U.S.C. §103(e) is improper and respectfully request that the rejection should be withdrawn.

CONCLUSION

Applicant respectfully requests that the remarks of the present response be entered and made of record in the present application. Applicant submits that the claims fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections is respectfully requested. It is estimated that no additional fee is required for filing this Amendment. However, should the Patent Office determine otherwise, please charge the necessary fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: April 1, 2005

Anthony M. Insogna 35,203
Anthony M. Insogna (Reg. No.)

By: Jacqueline Benn 43,492
Jacqueline Benn (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939

Enclosures